Patented Oct. 31, 1950

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UNITED STATES PATENT OFFICE

2,528,000

PROCESS OF PREPARING 2-CYANO-1-KETO-7-R-1,2,3,4-TETRAHYDROPHENANTHRENES, AND PRODUCTS OF SUCH PROCESS

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24 Claims. (Cl. 260—465)

1

The invention of this application is directed to the production of certain 2-cyano-1-keto-7-R-1,2,3,4-tetrahydrophenanthrenes, and to those compounds themselves; which are useful in the synthesis of steroids of the type in which both rings A and B are aromatic—and especially in the synthesis of equilenin and desoxyequilenin—and are produced by the third step of that synthesis.

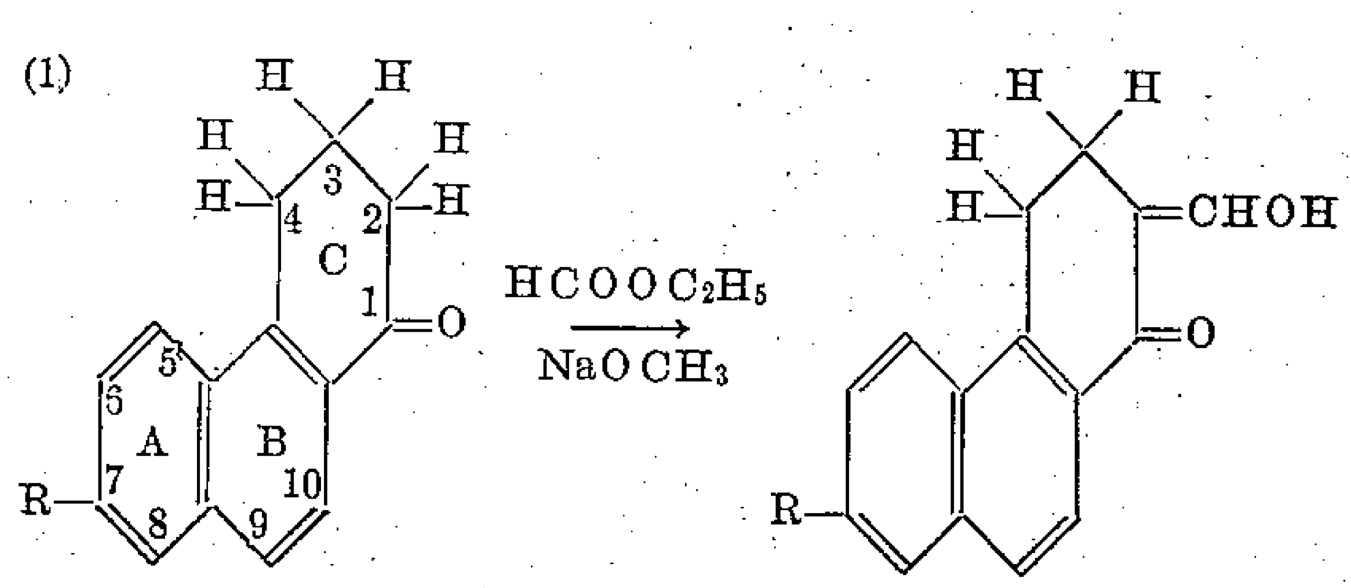
The complete synthesis of these steroids involves five steps; which, however, except as will be indicated, we believe to be individually new. The claims of the present application are directed specifically to the third step, and to the products obtained thereby; and the first, second, fourth, and fifth steps form the subject-matter of four separate applications, respectively. The present application is a division, as are three of said four companion applications, of the fourth of those companion applications; which is directed specifically to the fifth step of the synthesis, and which is Serial No. 700,380, filed October 1, 1946. The filing of the divisional applications is in response to a requirement for division by the Patent Office, made in such parent application Serial No. 700,380, in which all five steps and their products were originally claimed.

Because the claims of the present application are limited to the third step of the complete synthesis, only that step will be described in full detail in this application; and the other four steps will be set forth only in that general description.

The five steps of the complete synthesis of the steroids are as follows:

a. 1-keto-7-R-1,2,3,4-tetrahydrophenanthrene, in which R indicates a substituent in the class consisting of hydrogen and lower-alkoxy groups (including lower-aralkoxy groups), desirably either hydrogen or the methoxy group, is condensed with a lower-alkyl formate, conveniently ethyl formate, in the presence of sodium methoxide, and desirably in an inert solvent, such as benzene for example; to produce 1-keto-2-hydroxymethylene-7-R-1,2,3,4 - tetrahydrophenanthrene, as follows:

(1)



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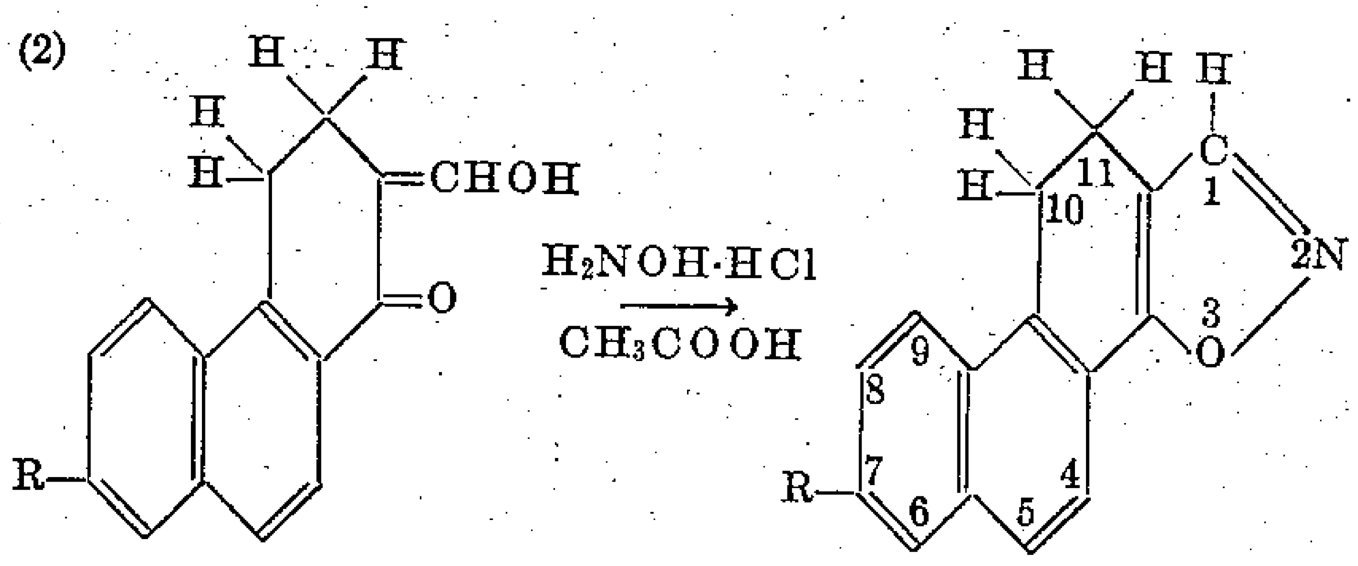
This product is new when R is an alkoxy or aralkoxy group, but not when R is hydrogen.

b. 1-keto - 2 - hydroxymethylene-7-R-1,2,3,4-tetrahydrophenanthrene is treated with hydroxylamine, desirably as the hydrochloride dissolved in acetic acid; to produce 10,11-dihydro-7-R-phenanthro[2,1-d]isoxazole, as follows:

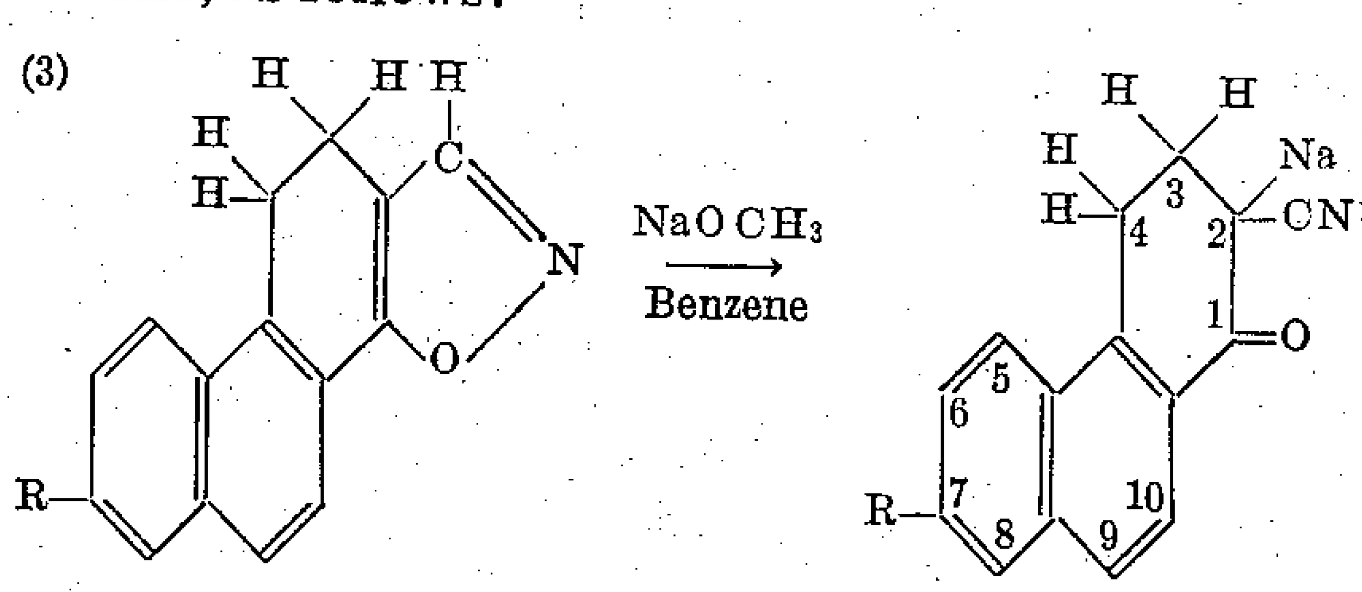
(2)



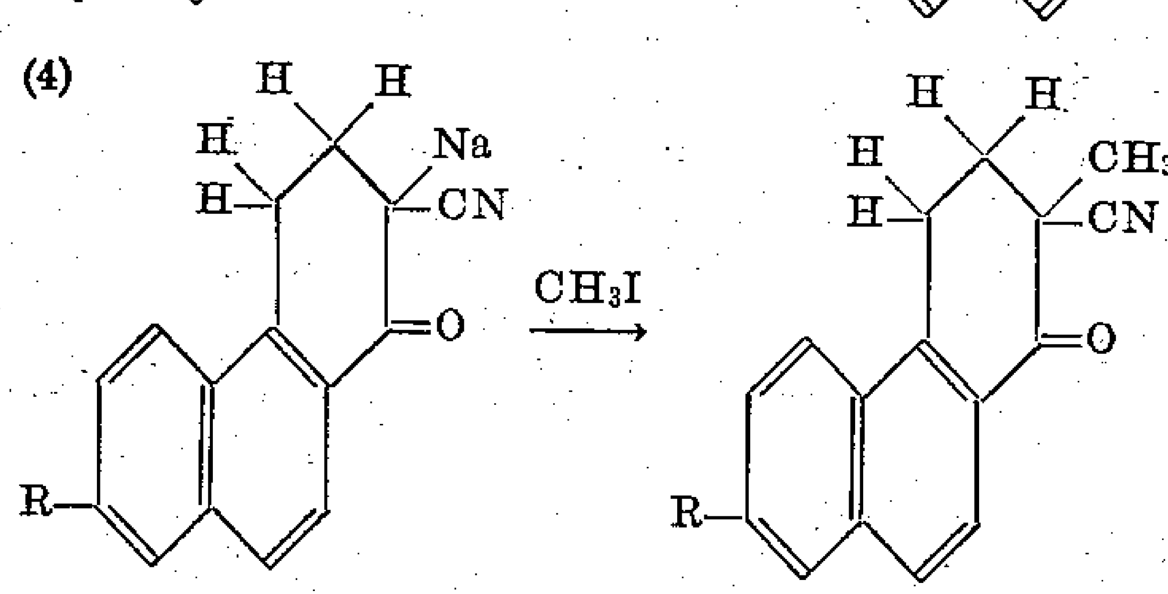
This product is new.

c. The 10,11-dihydro-7-R-phenanthro[2,1-d]-isoxazole, desirably in an inert solvent, benzene for example, is treated with an alkali-metal alkoxide, conveniently sodium methoxide, followed by a methyl heavy-halide, preferably methyl iodide but premissibly methyl bromide; to produce (first) 2-cyano-1-keto-7-R-2-sodio-1,2,3,4-tetrahydrophenanthrene, which is commonly not isolated, and (second) 2-cyano-1-keto-7-R-2 - methyl - 1,2,3,4-tetrahydrophenanthrene, as follows:

(3)



(4)



The products obtained by reactions 3 and 4 are new.

By treating the product of reaction 3 with a mineral acid, we can get a modification in which a hydrogen atom takes the place of the sodium atom; and, if desired, that modified product, after being treated with sodium methoxide, may be used as the starting point for reaction 4.

d. The 2-cyano-1-keto-7-R-2-methyl-1,2,3,4-tetrahydrophenanthrene is condensed with a di-lower-alkyl succinate, preferably dimethyl succinate, in the presence of an alkali-metal tertiary-lower-alkoxide, conveniently potassium tertiary-butoxide; preferably followed by treatment with a mineral acid, for instance hydrochloric acid; to produce a 15-carboalkoxy-14,15-dehydro-equilenin ether or 15-carboalkoxy-14,15-dehydro-desoxyequilenin, according to whether R is a radical or hydrogen; and the product so obtained is hydrolyzed, desirably with barium hydroxide followed by hydrochloric acid, to give the free acid, a 15-carboxydehydroequilenin ether or 15-carboxy-dehydro-desoxyequilenin.

The products so obtained are new.

e. This free acid, 15-carboxy-dehydroequilenin ether or 15-carboxy-dehydrodesoxyequilenin, is decarboxylated by heating under reduced pressure; to produce a mixture of two isomeric dehydroequilenin ethers or a mixture of two isomeric dehydrodesoxyequilenins according to whether R is a radical or hydrogen. The isomers of each pair differ by having a double bond in the 14,15-position on the one hand and in the 15,16-position on the other. This product, with or without separating its component isomers, is hydrogenated, desirably over a palladium-charcoal catalyst, to produce two compounds, one of which is a racemic equilenin ether or a racemic desoxyequilenin and the other of which is a racemic isoequilenin ether or a racemic desoxyisoequilenin, in each case according to whether R is a radical or hydrogen. The two compounds so produced are stereoisomers in each case. These two compounds are separated, as by fractional crystallization. In the case where R is hydrogen, this separation gives directly d,l-desoxyequilenin and d,l-desoxyisoequilenin. In the case where R is methoxy, the separated compounds are demethylated, by known methods, to obtain respectively d,l-equilenin and d,l-isoequilenin. The d,l-equilenin is resolved, by known methods, to obtain d-equilenin, which is found to be identical with natural equilenin.

The following are examples of the process of the present application, and the products obtained thereby—obtained by the first three of the five steps of the complete steroid synthesis. The melting points given are all corrected for stem exposure.

Example 1.—The preparation of 2-cyano-1-keto-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene, useful for preparing equilenin

To a suspension of powdered sodium methoxide (prepared by dissolving 3.39 g. of sodium in methanol, removing excess methanol by evaporation under reduced pressure, and heating at approximately 200° C. for one hour under high vacuum), in 70 cc. of dry benzene, is added 10.90 g. of ethyl formate; after which is added a solution of 16.54 g. of 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene in 110 cc. of benzene. The system containing the mixture is evacuated; and then filled with nitrogen, and allowed to stand at room temperature for about 5 hours, with occasional swirling. A copious yellow precipitate is formed. This precipitate is dissolved by shaking with ether and ice water, and then allowing the whole to separate into two layers. The water layer, which contains the 1-keto-7-methoxy-2-hydroxymethylene-1,2,3,4-tetrahydrophenanthrene in the form of the sodio derivative, is separated from the ether layer and preserved; and for complete recovery the ether layer is desirably washed thoroughly with water and with dilute potassium hydroxide solution and the washings added to the separated aqueous layer. The combined aqueous solution is then acidified, to cause separation of the 1-keto-2-hydroxymethylene-7-methoxy-1,2,3,4-tetrahydroxyphenanthrene, as yellow crystals. As first obtained, these give a yield of about 17.73 g. (or 95%), melting at about 130–131.5° C.; which is of satisfactory purity for the next step. The crystals may be purified if desired, as by recrystallization several times with alcohol; but the melting point is not materially changed, although somewhat sharpened, for the recrystallized crystals have a melting point of 130–130.6° C.

Analysis shows the following: Calculated for $C_{16}H_{14}O_3$: C, 75.57%; H, 5.55%. Found: C, 75.37%; H, 5.68%.

The yellow crystalline 1-keto-2-hydroxymethylene-7-methoxy-1,2,3,4-tetrahydrophenanthrene thus obtained is used as the starting point for the next step. The 17.73 g. of that hydroxymethylene ketone is dissolved in about 400 cc. of glacial acetic acid, and the solution is stirred with 7.25 g. of dry powdered hydroxylamine hydrochloride at about 68–70° C. (the temperature of solution) for about 7 hours. The solution becomes pink. The hot pink solution is diluted with about an equal volume of hot water to the point of incipient cloudiness, and then allowed to cool; and on such cooling a deposit is obtained of usually colorless (although sometimes colored) crystals of 10,11-dihydro-7-methoxyphenanthro [2,1-d] isoxazole. The yield is about 15.81 g. (or about 90%), after drying at 100–110° C. The melting point is about 137–138° C., with softening preceding melting. Purification may be obtained by evaporative distillation at 150° C. at 0.5 to 1 mm. pressure, followed by recrystallization from a mixture of methanol and ethyl acetate; which gives colorless crystals melting at 139.5–140° C.

Analysis shows the following: Calculated for $C_{16}H_{13}O_2N$: C, 76.47%; H, 5.21%. Found: C, 76.71%; H, 5.07%.

The crude isoxazole may contain a small amount of a benzene-insoluble material, possibly a phenolic product resulting from demethylation; but is nevertheless sufficiently pure for the next step.

The above procedure may be conveniently altered in the following way: A mixture of 16.87 g. of the crude 1-keto-2-hydroxymethylene-7-methoxy-1,2,3,4-tetrahydrophenanthrene, 400 cc. of glacial acetic acid, and 6.91 g. of hydroxylamine hydrochloride, is quickly heated to boiling in an oil bath maintained at about 170° C. The refluxing is then continued for about 7 minutes, whereupon the solution (which is now red) is diluted with hot water until definitely turbid. The whole is then allowed to cool several hours in an ice box, during which time crystallization of the 10,11-dihydro-7-methoxyphenanthro [2,1-d] isoxazole occurs. The isoxazole as thus obtained is in the form of tan-colored plates melting at about 137–138° C., and the yield is about 15.80 g. (about 95%).

The next step may be either in two parts or in one part.

If it is in two parts, it is as follows:

FIRST PART

To a cool solution of 0.9 g. of sodium in 11 cc. of methanol is added a filtered solution of 6.66 g. of the crude 10,11-dihydro-7-methoxyphenanthro [2,1-d] isoxazole in 80 cc. of dry benzene. The mixture is stirred during the addition, which should take about 10 minutes, and then is stirred for about 3 hours longer, all at room temperature. Ether is added, and the mixture is shaken with successive portions of water (desirably about 1.5 liters in all). The water dissolves the product of the reaction, which is 2-cyano-1-keto-7-methoxy-2-sodio-1,2,3,4-tetrahydrophenanthrene and is sparingly water-soluble. The water and ether layers are allowed to stand, so that they separate; and the water layers are removed and preserved. For increased yield, the ether layer is desirably extracted with dilute potassium hydroxide solution, and the extract is combined with the separated water layers. The combined aqueous extract is then acidified, as with hydrochloric acid; and gives about 6.23 g. (94% yield) of a yellow solid, 2-cyano-1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene, melting at about 164–168.5° C. Although this is sufficiently pure for the remainder of the process, it may be purified; as by vacuum sublimation, followed by recrystallization from alcohol, to give yellow plates melting at 169.5–171° C. Analysis of the purified product shows the following:

Calculated for $C_{16}H_{13}O_2N$: C, 76.47%; H, 5.21%. Found: C, 76.28%; H, 5.38%.

SECOND PART

For this part, 6.00 g. of the crude 2-cyano-1-keto-7-methoxy-1,2,3,4 - tetrahydrophenanthrene and 30 cc. of dry benzene are added to a solution of 2.64 g. of sodium in 50 cc. of methanol; and the whole is refluxed for 15 minutes, with stirring. The mixture is cooled, 8 cc. of methyl iodide is added, and the stirring is continued at room temperature for about 45 minutes. Then an additional 8 cc. of methyl iodide is added, and the stirring is continued until solution is practically complete, which usually takes about 2 or 3 hours. The solution is then heated under reflux conditions, for about 2 hours, to complete the reaction; and a few drops of acetic acid are added to neutralize the mixture, after which most of the solvent is removed by evaporation in a current of air. Then about 100 cc. of water is added; after which the product is extracted with a mixture of benzene and ether, the organic layer is separated from the water layer, and the solution thus obtained is successively washed thoroughly with water, several portions of dilute potassium hydroxide solution, and saturated salt solution. The benzene-ether solution is then dried over anhydrous potassium carbonate; and then the solvent is removed by evaporation to leave a solid residue; which is crystallized from alcohol. This gives about 5.05 g. (an 80% yield) of pale yellow crystals, melting at about 132.5–134.5° C. preceded by a softening at about 130° C. This product, which is 2 - cyano - 1 - keto - 7 - methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene, is sufficiently pure for use for the remainder of the process. The yellow crystals may be purified if desired, however, by evaporative distillation at 150° C. under a pressure of 0.5 to 1 mm., followed by recrystallization from ethyl acetate; which gives colorless needles melting at 135–137.5° C. Analysis of the purified product shows the following: Calculated for $C_{17}H_{15}O_2N$: C, 76.96%; H, 5.70%. Found: C, 77.10%; H, 5.90%.

If it is desired to produce the 2-cyano-1-keto-7-methoxy-2-methyl-1,2,3,4 - tetrahydrophenanthrene in one step from the 10,11-dihydro-7-methoxyphenanthro [2,1-d] isoxazole, it may be done by direct methylation as follows:

To a cool solution of 7.5 g. of sodium in 65 cc. of methanol is added, with stirring, a solution of 10.0 g. of the crude isoxazole in 100 cc. of dry benzene. The addition is made slowly, so that it takes about 20 minutes. The sodio derivative of the desired cyano compound is formed, as indicated by the appearance of a yellow precipitate. The mixture is then stirred at room temperature for about 45 minutes. Then 15 cc. of methyl iodide is added, without any preliminary separation, and the mixture is stirred for about 1 hour; and then 10 cc. of methyl iodide is introduced, and the stirring is continued for about one-half hour. Then 5 cc. of methyl iodide is added, and the whole is refluxed for about 2½ hours, and the solution is worked up as described in the preceding two-step process following the addition of the methyl iodide. In this one-step method, the 2-cyano-1-keto-7-methoxy - 2 - methyl - 1,2,3,4-tetrahydrophenanthrene is obtained directly as almost colorless crystals, melting at about 135–137° C., with a yield of about 9.25 g., or about 88% of the theoretical amount.

A second crop of crystals may if desired be obtained from the mother liquor. These crystals are undoubtedly a mixture, melting at about 100–120° C., and we are not sure what they are.

The 2-cyano-1-keto-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene, whether obtained by the two-step or the one-step process, may be used as the starting point for the remaining two steps of the synthesis; which are outlined in the general description given above and are set forth in detail in the companion applications above referred to, and which lead to the production of equilenin.

Example 2.—The preparation of 2-cyano-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene, useful for preparing desoxyequilenin.

To a suspension of powdered sodium methoxide, (prepared by dissolving 1.28 g. of sodium in methanol, removing the excess methanol by evaporaton under reduced pressure, and heating at approximately 200° C. for 1 hour under high vacuum), in 100 cc. of dry benzene, is added 4.12 g. of ethyl formate; after which is added a solution of 5.40 g. of 1-keto-1,2,3,4-tetrahydrophenanthrene in 50 cc. of benzene. The system containing the mixture is evacuated, and then filled with nitrogen and allowed to stand at room temperature for about four hours, with occasional swirling. During this time the mixture very slowly assumes a slight pink tinge and gradually becomes very viscous. Cold water is then added, followed by a small amount of ether to minimize formation of emulsions, and the whole is shaken well and then allowed to separate into two layers. The water layer, which contains 1-keto-2-hydroxymethylene - 1,2,3,4 - tetrahydrophenanthrene in the form of its sodio derivative, is separated from the ether layer and preserved; and for complete recovery the ether layer is desirably washed thoroughly with water and with dilute potassium hydroxide solution and the washings added to the separated aqueous layer. The combined aqueous solution is then acidified, to cause the separation of the 1-keto-2-hydroxymethylene-1,2,3,4-tetrahydrophenanthrene, as a light-yellow solid. The yield of this product is about 5.82 g. (or 94%), and the melting point is about 82–83° C. This corresponds fairly closely with the melting point reported by Meyer and Reichstein for the same compound produced by a different procedure. See Pharmaceutical Acta Helvetiae, vol. 19, page 128 et seq., published in 1944.

The 1-keto-2-hydroxymethylene-1,2,3,4-tetrahydrophenanthrene thus obtained is used as the starting point for the next step: 21.5 g. of that hydroxymethylene ketone is dissolved in about 410 cc. of glacial acetic acid, and the solution is stirred with 9.75 g. of dry powdered hydroxylamine hydrochloride at about 85° C. for about 6 hours. Sufficient crushed ice is then added to bring the volume of solution to about 2 liters. When the ice has melted, there is present a light pink solid, which is filtered off and dried in an oven at about 60° C. This solid is 10,11-dihydrophenanthro[2,1-d]isoxazole; it amounts to about 20 g. (a 94% yield), and has a melting point of about 104–107° C. This material is of satisfactory purity for the next step in the synthesis. Purification may be obtained if desired, by recrystallization from dilute alcohol; which gives colorless crystals melting at 109.8–110.5° C.

Analysis shows the following: Calculated for $C_{15}H_{11}ON$: C, 81.42%; H, 5.01%; N, 6.33%. Found: C, 81.71%; H, 4.90%; N, 6.48%.

The next step may be either in two parts or in one part.

If it is in two parts, it is as follows:

FIRST PART

To a cool solution of 3.2 g. of sodium in 40 cc. of methanol is added a solution of 20 g. of crude 10,11-dihydrophenanthro[2,1-d] isoxazole in 250 cc. of dry benzene. A yellow precipitate of 2-cyano-1-keto-2-sodio-1,2,3,4-tetrahydrophenanthrene separates as the solution is allowed to stand at room temperature for about 30 minutes. Ether is added, and the mixture is shaken with about 1 liter of water. The water and ether layers are allowed to stand, so that they separate; and the water layer is removed and preserved. In order to recover more material from the ether layer, it is washed with successive portions of dilute sodium hydroxide (desirably a total of about 4 liters), and these washings are all combined with the aqueous extract and then acidified, as with hydrochloric acid. This gives about 18.8 g. (a 95% yield) of light tan 2-cyano-1-keto-1,2,3,4-tetrahydrophenanthrene, melting at about 125–126.5° C. Although this is sufficiently pure for the remainder of the process, it may be purified by recrystallization from dilute alcohol, which gives colorless plates melting at 128–129° C.

The analysis shows: Calculated for $C_{15}H_{11}ON$: C, 81.42%; H, 5.01%; N, 6.33%. Found: C, 81.68%; H, 4.96%; N, 6.39%.

SECOND PART

For the next step, 18.8 g. of the crude 2-cyano-1-keto-1,2,3,4-tetrahydrophenanthrene dissolved in 67 cc. of warm benzene is added to a solution of 7.3 g. of sodium in 110 cc. of methanol; and the whole is refluxed for 15 minutes, with stirring. The mixture is cooled, 11 cc. of methyl iodide is added, and the stirring is continued at room temperature for about 45 minutes. Then an additional 11 cc. of methyl iodide is added, and the solution is allowed to stand for about 30 minutes. Finally 5 cc. more of methyl iodide is added, and the solution is refluxed for 1½ hours to complete the reaction. The solvents are then removed under reduced pressure, and the residue is dissolved in benzene and is washed thoroughly with several portions of dilute potassium hydroxide solution. The benzene solution is then dried over anhydrous potassium carbonate; and the solvent is removed by evaporation to leave a solid residue, which is crystallized from methanol. This gives a total of about 16.7 g. (a yield of 83%) of material melting at about 121–127° C. This product is 2-cyano-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene, and is sufficiently pure for use for the remainder of the process. The material may be purified if desired, however, by recrystallization from methanol; which gives colorless plates melting at 126–127° C. Analysis of the purified product shows the following: Calculated for $C_{16}H_{13}ON$: C, 81.67%; H, 5.57%. Found: C, 81.70%; H, 5.58%.

If it is desired to produce the 2-cyano-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene in one step from the 10, 11 dihydrophenanthro[2,1-d]-isoxazole, it may be done by direct methylation as follows:

To a cool solution of 0.6 g. of sodium in 28 cc. of methanol is added a solution of 4.7 g. of the crude isoxazole in 17 cc. of benzene. This solution is allowed to stand for 30 minutes at room temperature, and is then refluxed for 10 minutes and cooled. To this cool solution is now added 3 cc. of methyl iodide; and the mixture is shaken, and then allowed to stand at room temperature for 1 hour. A second portion (2 cc.) of methyl iodide is then added, and the solution is allowed to stand for 2 hours at room temperature, and then is refluxed for 4 hours. The reaction mixture is worked up as described in the preceding 2-step process following the addition of the methyl idodide. In this 1-step method, the 2-cyano-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene is obtained directly in about 91% yield. The weight is about 4.55 g. and the melting point is about 124.5-126° C.

The 2-cyano-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene, whether obtained by the 2-step process or the 1-step process, may be used as the starting point for the remaining two steps of the complete synthesis; which are outlined in the general description given above and are set forth in detail in the companion applications above referred to, and which lead to the production of desoxyequilenin.

We claim as our invention:

1. The process of making a 2-cyano-1-keto-7-R-2-methyl-1,2,3,4-tetrahydrophenanthrene, in which R is a lower alkoxy group, which consists in treating a 10,11-dihydro-7-R-phenanthro [2,1-d] isoxazole with an alkali-metal lower alkoxide under substantially anhydrous conditions, followed by a methyl heavy-halide.

2. The process as set forth in claim 1, in which the treatment is done in an inert solvent.

3. The process as set forth in claim 1, in which the alkali-metal lower alkoxide is sodium methoxide.

4. The process as set forth in claim 1, in which the methyl heavy-halide is methyl iodide.

5. A 2-cyano-1-keto-7-R-2-methyl-1,2,3,4-tetrahydrophenanthrene, in which R is a lower-alkoxy group.

6. 2-cyano-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene.

7. 2-cyano-1-keto-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene.

8. The process of making a 2-cyano-1-keto-7-R-1,2,3,4-tetrahydrophenanthrene, in which R is a lower-alkoxy group, which consists in treating a 10,11-dihydro-7-R-phenanthro[2,1-d]isoxazole

with an alkali-metal lower alkoxide under substantially anhydrous conditions, followed by a mineral acid.

9. The process as set forth in claim 8, in which the treatment is done in an inert solvent.

10. The process as set forth in claim 8, in which the alkali-metal alkoxide is sodium methoxide.

11. A 2-cyano-1-keto-7-R-1,2,3,4-tetrahydrophenanthrene, in which R is a lower-alkoxy group.

12. 2-cyano-1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene.

13. The process of making a 2-cyano-1-keto-7-R-2-methyl-1,2,3,4-tetrahydrophenanthrene, in which R is a lower-alkoxy group, which consists in treating a 2-cyano-1-keto-7-R-1,2,3,4-tetrahydrophenanthrene with an alkali-metal lower alkoxide under substantially anhydrous conditions, followed by a methyl heavy-halide.

14. The process as set forth in claim 13, in which the treatment is done in an inert solvent.

15. The process as set forth in claim 13, in which the alkali-metal alkoxide is sodium methoxide.

16. The process as set forth in claim 13, in which the methyl heavy-halide is methyl iodide.

17. In the process of making a 2-cyano-1-keto-7-R-1,2,3,4-tetrahydrophenanthrene having in the 2 position a member of the class consisting of hydrogen and the methyl group, and in which R is a member of the class consisting of hydrogen and lower-alkoxy groups, the step which consists in treating a compound of the class consisting of a 10,11-dihydro-7-R-phenanthro[2,1-d]isoxazole and a 2-cyano-1-keto-7-R-1,2,3,4-tetrahydrophenanthrene with an alkali-metal lower alkoxide under substantially anhydrous conditions.

18. In the process of making a 2-cyano-1-keto-7-R-2-methyl-1,2,3,4-tetrahydrophenanthrene, in which R is a lower-alkoxy group, the steps which consist in treating a compound of the class consisting of a 10,11-dihydro-7-R-phenanthro[2,1-d]isoxazole and a 2-cyano-1-keto-7-R-1,2,3,4-tetrahydrophenanthrene with an alkali-metal lower alkoxide under substantially anhydrous conditions, followed by a methyl heavy-halide.

19. A 2-cyano-1-keto-7-R-1,2,3,4-tetrahydrophenanthrene, having in the 2 position a member of the class consisting of hydrogen and the methyl group, and in which R is a member of the class consisting of hydrogen and lower-alkoxy groups.

20. The process step as set forth in claim 17, in which the treatment is done in an inert solvent.

21. The process step as set forth in claim 17, in which the alkali-metal alkoxide is sodium methoxide.

22. The process step as set forth in claim 17, in which the methyl heavy-halide is methyl iodide.

23. The process of making 2-cyano-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene, which consists in treating 10,11-dihydrophenanthro[2,1-d]isoxazole with an alkali-metal lower alkoxide under substantially anhydrous conditions, followed by a methyl heavy-halide.

24. The process of making 2-cyano-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene, which consists in treating 2-cyano-1-keto-1,2,3,4-tetrahydrophenanthrene with an alkali-metal lower alkoxide under substantially anhydrous conditions, followed by a methyl heavy-halide.

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REFERENCES CITED

The following references are of record in the file of this patent:

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Certificate of Correction

Patent No. 2,528,000 October 31, 1950

WILLIAM S. JOHNSON ET AL.

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction as follows:

Column 10, line 14, for the claim reference numeral "17" read *18*; and that the said Letters Patent should be read as corrected above, so that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 20th day of February, A. D. 1951.

[SEAL]

THOMAS F. MURPHY,
Assistant Commissioner of Patents.